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Review

The clinical anti-inflammatory effects and underlying mechanisms of silymarin

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SUMMARY

Inflammatory conditions are key mediators in the progression of various diseases. Silymarin, derived from *Silybum marianum* seeds and fruits, has shown efficacy in treating a range of liver diseases. The expanding corpus of research on silymarin highlights its promising role in preventing and managing inflammatory conditions and autoimmune without adverse effects. This review discusses the absorption, metabolism, and anti-inflammatory mechanisms of silymarin, exploring its impact on the secretion of inflammatory factors, such as nuclear factor kappa B (NF-κB) pathway, mitogen-activated protein kinase (MAPK) pathway, and antioxidant pathway. We delve into its disease-modifying potential for clinical applications, thereby laying a theoretical foundation for further silymarin research and clinical studies.

INTRODUCTION

Silymarin, primarily sourced from *Silybum marianum* (milk thistle), is a distinguished medicinal herb within the Asteraceae family.[1] Esteemed for the distinctive white veins on its leaves, milk thistle has been harnessed as a natural remedy for over two millennia, celebrated for its hepatoprotective qualities.[2] The silymarin complex, extracted from the plant's seeds and fruits, is rich in flavonolignans, flavonoids, and polyphenols.[3] Silibinin, constituting approximately 50%–60% of this complex, along with other flavonolignan isomers, accounts for about 35%, forming the crux of silymarin's therapeutic potency.[4,5] Identified in 1959 as a pioneering member of the flavonolignan family,[6] silibinin exists in two diastereoisomers: silibinin A and silibinin B (Figure 1).[7] *Silybum marianum* has a storied history of use in herbal medicine, demonstrating efficacy against a spectrum of liver conditions, including chronic liver disease, cirrhosis, and hepatocellular carcinoma.[8,9] Furthermore, recent research underlines silymarin's promising capacity as an anti-inflammatory agent, expanding its potential clinical applications beyond hepatoprotection.[10–12]

The interplay between inflammation and disease is complex, often resulting in a feedback loop that exacerbates both conditions and presents significant challenges to treatment strategies.[13,14] Traditional anti-inflammatory pharmacotherapy, such as aspirin, ibuprofen, naproxen, and indomethacin, targets the cyclooxygenase (COX) enzymes, pivotal in the biosynthesis of prostaglandins (PGs).[15] PGs are instrumental in the manifestation of symptoms such as fever, pain, and inflammation.[16] While effective in mitigating inflammation, these medications are associated with a notable risk of adverse effects, including gastrointestinal irritation and complications.[17] In contrast, silymarin, a bioactive compound extracted from the milk thistle plant (*Silybum marianum*), has emerged as a potent natural alternative with promising therapeutic efficacy against various conditions, including liver disease, neurotoxicity, and colorectal cancer.[18,19] Its anti-inflammatory properties, attributed to mechanisms distinct from those of conventional drugs, offer the potential for disease treatment with a lower incidence of side effects.[20] This review synthesizes recent findings on the anti-inflammatory actions of silymarin and its clinical applications, highlighting its significance as one of the most promising natural compounds for disease management.

ABSORPTION AND METABOLISM OF SILYMARIN

Optimal pharmacokinetic properties, including absorption, distribution, metabolism, and excretion, are crucial for drugs to exert therapeutic actions within the body effectively.[21] Commonly used non-steroidal anti-inflammatory drugs typically exhibit prolonged half-lives, extending beyond 8 h, with ibuprofen demonstrating a shorter half-life of approximately 4–5 h.[22] These anti-inflammatory agents are characterized by high bioavailability and stability, facilitating their widespread use.[23] Although silymarin has been recognized as a potential anti-inflammatory agent, its low water solubility and inefficient absorption limit its therapeutic efficacy in anti-inflammatory applications.[24] Addressing the bioavailability and stability of silymarin has thus emerged as a critical focus of research, laying the groundwork for the development of novel silymarin-based formulations.[25] Recent advancements have highlighted the potential of nanotechnology-based platforms to enhance the

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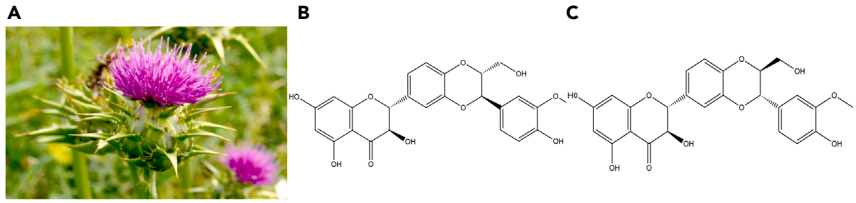

Figure 1. *Silybum marianum* and chemical structure of silibinin

(A) *Silybum marianum*.

(B) Silibinin A.

(C) Silibinin B. Source: https://baike.so.com/.

delivery of poorly water-soluble active ingredients.[26] Techniques such as nano-encapsulation have been employed to improve the solubility of silymarin, facilitating its encapsulation in aqueous nanocarriers.[27] This approach enhances passive absorption through the intestinal lumen into the lymphatic and circulatory systems, significantly increasing oral bioavailability. At the same time, the biological availability and bioactivity of silibinin can be enhanced through the use of solution-enhanced dispersion by supercritical fluids.[28] In addition, the complex formed by silymarin and natural cyclodextrin and the complex formed by silymarin and phospholipid can also significantly improve the bioavailability of silymarin.[29] Consequently, these innovations offer promising avenues to augment the anti-inflammatory efficacy of silymarin, showcasing the potential of modern science and technology in overcoming pharmacokinetic barriers.

POTENTIAL ANTI-INFLAMMATORY PATHWAYS OF SILYMARIN

Inhibition of inflammatory factor secretion

Silymarin has demonstrated profound anti-inflammatory effects through the modulation of cytokines, evidenced by the reduction of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), IL-6, tumor necrosis factor alpha (TNF-α), and interferon-γ in serum and liver tissues.[30,31] Concurrently, it elevates the levels of anti-inflammatory cytokines, including IL-10 and IL-12, underscoring its significant therapeutic potential.[32] The inflammasome, a protein complex pivotal in initiating inflammatory responses to pathogens and cellular damage, is key to understanding silymarin's mechanism.[33] The complex responds to pathogen-associated molecular patterns and damage-associated molecular patterns, particularly IL-1β and IL-18, which are efficiently downregulated by silymarin.[30] Of particular note, IL-1β is a central mediator in various inflammatory pathways.[34] The production and release of IL-1β is regulated by caspase-1,[35] which is also responsible for activating IL-18 and facilitating the secretion of other inflammatory proteins like IL-1α and fibroblast growth factor 2 through non-traditional pathways.[34] This cascade of events amplifies the inflammatory response, highlighting the inhibitory effects of silymarin on these processes. In experimental models, silymarin was reported to reduce the levels of the cytokine IL-8 in mice with airway inflammation induced by cigarette smoke extract, indicating dose-dependent anti-inflammatory effects. Moreover, its beneficial effects extend to reducing pro-inflammatory mediators in H292 human airway epithelial cells following stimulation with silica nanoparticles, highlighting its potential in preventing inflammatory cell infiltration into lung tissues.[36] Furthermore, silibinin, a major component of silymarin, undergoes oxidation to form 2,3-dihydro-silibinin, further inhibiting the release of lipopolysaccharide (LPS)-induced pro-inflammatory cytokines such as IL-6 and IL-8.[37] Additionally, the combination of silibinin, another active constituent of silymarin, with capsaicin has been shown to more effectively suppress LPS-induced TNF-α and IL-6 production than either compound alone, suggesting a synergistic effect in modulating inflammation.[38]

Nuclear factor kappa B pathway

Silibinin exhibits significant anti-inflammatory effects by attenuating the activity of proteins associated with inflammatory vesicles, such as nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 1 (NLRP1), NLRP3, and caspase-1, and modulating the genes' expression related to the nuclear factor kappa B (NF-κB) pathway, including Toll-like receptor 4, myeloid differentiation primary response 88, or mitogen-activated protein kinase (MAPK).[39] This modulation leads to a reduction in the activation and nuclear concentration of NF-κB, a critical transcription factor in inflammatory responses.[40] The NF-κB/Rel family, encompassing NF-κB1 (p50/p105), NF-κB2 (p52/p100), p65 (RelA), RelB, and c-Rel, plays a vital role in regulating genes linked to inflammation.[41] Activation of NF-κB involves the release of p65 from its inhibitory complex and its subsequent translocation to the nucleus, promoting the expression of pro-inflammatory genes.[42] Experimental evidence has shown that pre-treatment with silibinin, either alone or combined with capsaicin, can significantly reduce LPS-induced activation of NF-κB, with a combination of both demonstrating a more pronounced inhibitory effect on NF-κB activation.[38] Silibinin's supplementation has been noted to decrease IL-6 levels and mitigate renal carcinogenesis induced by diethylnitrosamine/2-acetylaminofluorene/carbon tetrachloride through the inhibition of p65 and inhibitor kappa B alpha (IκB-α) phosphorylation, indicating its potent NF-κB inhibitory properties.[40] Beyond renal cancer, silibinin's anti-inflammatory capabilities extend to various diseases.[43] It has been identified as an effective agent in managing the inflammatory response in conditions such as preeclampsia, lung inflammation, and *H. pylori*-induced gastritis, primarily through the inhibition of the NF-κB and NLRP3 signaling pathways and the suppression of COX-2 and inducible nitric oxide synthase (iNOS) expression.[33,44,45] Furthermore, silibinin has shown potential in reducing oxidative stress and inflammation in

nonalcoholic steatohepatitis (NASH) induced by a methionine-choline-deficient diet,[46] as well as alleviating hepatic ischemia-reperfusion injury,[47] by modulating lipid metabolism and downregulating NF-κB and NLRP3 expression.

MAPK pathway

Silymarin targets the MAPK pathway, a crucial upstream regulator of NF-κB, to exert its anti-inflammatory effects.[48] MAPK activation involves its translocation into the nucleus, where it phosphorylates several key transcription factors, notably nuclear factor erythroid 2-related factor 2, NF-κB, and activator protein-1.[49,50] This pathway is instrumental in regulating a broad spectrum of biological processes, such as cell proliferation, differentiation, apoptosis, inflammation, and the cellular response to environmental stressors.[51] The MAPK family comprises various stress-responsive kinases, including c-Jun N-terminal kinases (JNK), extracellular signal-regulated kinases (ERK), big MAP kinase 1, and p38 MAP kinase.[52] Previous study demonstrated that exposure to D-galactosamine/LPS elevates NF-κB and p38 expression in mice, suggesting the activation of inflammatory pathways.[32] Silymarin administration leads to a significant reduction in these inflammatory markers and an increase in IκB-α expression in hepatic tissue, indicating its potential to mitigate liver inflammation and injury.[53] Moreover, COX-2, which associated with inflammatory responses, is notably decreased following silymarin treatment as well.[54] By the way, silymarin offers neuroprotection by inhibiting the phosphorylation of ERK1/2, JNK, and p38 MAPK and reducing the expression of the epidermal growth factor receptor and glial fibrillary acidic protein.[55] Immunohistochemical analyses reveal changes in the expression of phosphorylated ERK1/2, JNK, and p38 in silymarin-treated tissues compared to controls, affirming silymarin's modulatory influence on MAPK pathway components.[55] Beyond its effects on liver and neuronal tissues, silymarin displays anti-inflammatory actions in renal and pulmonary contexts. In kidneys, silibinin, a constituent of silymarin, mitigates cisplatin-induced nephrotoxicity by attenuating reactive oxygen species (ROS)-mediated MAPK pathway activation and enhancing Nfe2l1-mediated antioxidant responses.[56] This suggests a novel approach for addressing acute kidney injury associated with cisplatin treatment.[56] Additionally, silibinin inhibits the production of pro-inflammatory factors and adhesion molecules in lung microvascular endothelial cells exposed to *Aspergillus fumigatus* via the p38 MAPK pathway. Prolonged silymarin exposure also suppresses various pro-inflammatory mRNAs and signaling pathways, including NF-κB and forkhead box O, underscoring its comprehensive anti-inflammatory effects.[57]

Antioxidant defense pathways

Silymarin is recognized for its potent antioxidant capabilities, primarily achieved through the inhibition of key antioxidant enzymes and the prevention of free radical-induced DNA damage.[58,59] Its anti-inflammatory properties are closely linked to this antioxidant effect, notably through the suppression of pro-inflammatory signaling cascades.[2] A critical aspect of silymarin's anti-inflammatory mechanism involves the downregulation of iNOS, which is responsible for the elevated production of nitric oxide during inflammatory processes. By inhibiting iNOS expression, silymarin significantly contributes to mitigating the inflammatory response.[60] Additionally, silymarin has been shown to inhibit platelet aggregation triggered by extracellular arachidonic acid, further illustrating its anti-inflammatory effects.[61] This inhibition is achieved by interfering with the arachidonic acid metabolism, thereby reducing the synthesis of pro-inflammatory mediators.[61] Furthermore, arachidonic acid produces lipid peroxyl radicals and lipid peroxides that are more reactive, through the action of lipoxygenase-5 (5-LOX) by double oxygenation.[62] These highly reactive molecules are precursors to biologically active compounds, including leukotrienes, hydroxy fatty acids, and lipoxins, which play significant roles in the inflammatory process.[63,64] By the way, silymarin was reported to curb the formation of oxygen radicals and lipid peroxides.[65,66] Its anti-inflammatory effects were shown by inhibiting 5-LOX activity and obstructing the lipid peroxidation pathway to prevent the generation of ROS involved in inflammatory responses.[67] Through these mechanisms mentioned earlier, silymarin was shown to protect cellular components from oxidative stress and mitigate inflammation, emphasizing its therapeutic potential in conditions characterized by oxidative stress and inflammation. The anti-inflammatory mechanism of silymarin is shown in Figure 2.

CLINICAL APPLICATIONS OF SILYMARIN AS AN ANTI-INFLAMMATORY AGENT

The anti-inflammatory properties of silymarin have been extensively shown in both preclinical and *in vitro* models, establishing its potential to mitigate disease via its anti-inflammatory effects.[45,68–71] Consequently, various research teams have progressed to applying silymarin in clinical trials aimed at treating conditions including radiotherapy-induced mucositis, radiation dermatitis, skin inflammation, diabetes, β-thalassemia major, and other diseases (Table 1; Figure 3).

Radiotherapy-induced mucositis

Radiation therapy, a cornerstone in cancer treatment, often leads to inflammatory side effects, such as mucositis.[93] In a landmark 2011 study by Altaei,[72] 65 patients undergoing chemotherapy-induced oral mucositis were enrolled in a randomized, double-blind, placebo-controlled trial. Participants were divided, with 23 receiving 140 mg/cap silymarin. The outcomes were promising; silymarin group exhibited significantly lower mean Oral Mucositis Assessment Scale and World Health Organization (WHO) Mucositis Scale scores, alongside visual analog scale scores, compared to both the indomethacin and placebo groups. Remarkably, within five days of silymarin treatment, all patients in this group showed signs of ulcer healing and reported pain relief. Additionally, there were significant reductions in serum levels of IL-1β and leptin, with an increase in trolox-equivalent antioxidant capacity, underscoring silymarin's anti-inflammatory and antioxidant efficacy against mucosal inflammation. Another study focusing on patients with head and neck cancer revealed that WHO Oral Mucositis Rating Scale and National

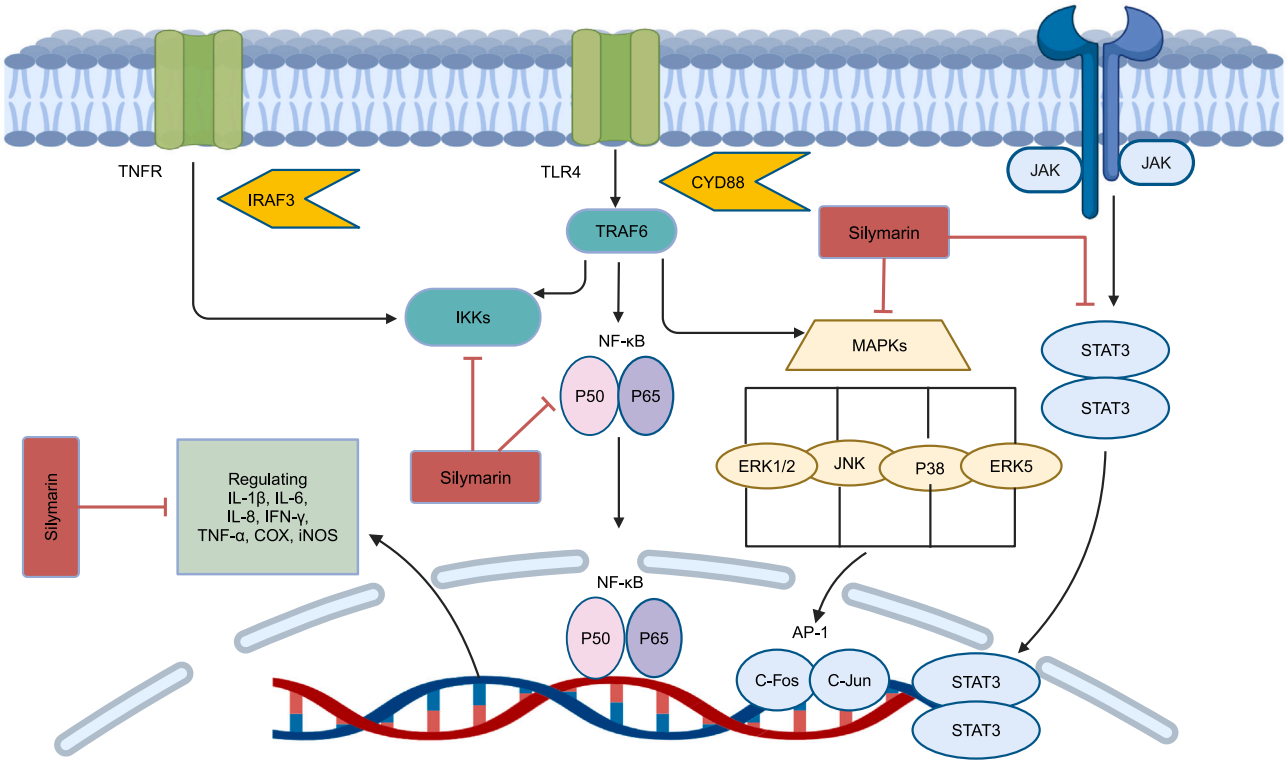

Figure 2. Anti-inflammatory molecular mechanism of silymarin

Silymarin improves inflammation by inhibiting the activation of NF-κB, MAPK, JAK-STAT3, and other pathways and regulating the secretion of inflammatory factors.

Cancer Institute Common Toxicology Criteria (NCI-CTC) mucositis scores were significantly lower in the silymarin-treated group compared to placebo ($p < 0.005$) during the first six weeks of radiotherapy.[73] This suggests that while silymarin may not outright prevent mucositis, it appears to slow its progression. A further trial investigating a silymarin nanosolution (210 mg/day) highlighted a decrease in European Organization for Research and Treatment of Cancer (EORTC) scale scores after the fourth week of treatment, suggesting potential benefits of adjusting treatment duration and formulation.[74]

Radiation dermatitis

Radiation dermatitis affects over 80% of patients with breast cancer undergoing postoperative radiotherapy, with about 10% developing grade 3 lesions.[75] A rigorous study evaluated the protective effects of 1% silymarin gel on dermatitis symptoms, using a randomized, double-blind, placebo-controlled design. The silymarin-treated group ($n = 40$) showed significantly lower median National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) and Radiation Therapy Oncology Group (RTOG) scores compared to placebo ($p < 0.05$), indicating reduced severity and delayed onset of dermatitis. Another clinical trial confirmed the efficacy of silymarin cream in mitigating both objective and subjective skin toxicity, with a higher percentage of patients assessed as normal when using silymarin cream throughout their radiotherapy period.[76] These findings advocate the prophylactic application of silymarin formulations that exert anti-inflammatory properties to significantly reduce the effects of radiation dermatitis.

Skin inflammation

Acne-prone skin is characterized by elevated oxidative stress and a diminished antioxidant defense compared to healthy skin.[94] This imbalance contributes to lipid peroxidation, inflammation, and the proliferation of acne-causing bacteria.[77] A comparative study evaluated the efficacy of 1.4% silymarin cream against 30% salicylic acid in treating mild to moderate acne vulgaris. Although no statistically significant difference was observed between the two treatments ($p = 0.377$), the silymarin cream demonstrated effectiveness and safety, paralleling the results of salicylic acid therapy. Another investigation involving 22 Korean participants using a 0.5% silymarin-loaded antioxidant serum for four weeks reported notable improvements in acne severity, as measured by the modified General Acne Grade Score, the General Acne Evaluation (GEA) scale, and a reduction in acne lesions.[78] Additionally, reductions in sebum production, skin pigmentation, and erythema were documented, with a significant change in the melanosis index. These findings suggest that silymarin's potential to manage mild to moderate acne could be attributed to its anti-inflammatory and antioxidant properties.

Table 1. Clinical applications of silymarin as an anti-inflammatory agent

Disease	Dose	Duration	Patients	Outcome	Reference
Oral mucositis	140 mg*3/day	14 days	65 patients	Healing time↓; serum IL-1β ↓; leptin levels↓; ulcer healing and pain relief↑	Altaei[72]
Mucositis	140 mg*3/day	6 weeks	27 patients	WHO and NCI-CTC scores↓; no grade 4 mucositis; significant median score differences.	Elyasi et al.[73]
Radiotherapy-induced mucositis	70 mg*3/day	6 weeks	31 patients	Median EORTC scores→ scores during radiation therapy↑	Hosseini et al.[74]
Radiation-induced dermatitis	1% silymarin	5 weeks	40 patients	Median NCI-CTCAE and RTOG scores↓; the onset and progression of radiation dermatitis were delayed	Karbasforooshan et al.[75]
Radiodermatitis	0.25% silymarin	4 weeks	101 patients	Median time to toxicity↑; incidence of radiodermatitis ↓	Becker-Schiebe et al.[76]
Acne vulgaris	0.5% silymarin	4 weeks	22 patients	Modified GAGS, GEA scores, and acne lesion counts↓; sebum secretion, skin pigmentation, and erythema↓	Atallah et al.[77]
Acne vulgaris	1.4% silymarin	3 months	30 patients	GAGS both facial sides↓; two instances of hyperpigmentation on the salicylic acid-treated side; no side effects observed	Kim et al.[78]
Liver injury	140 mg*3/day	14 days	90 patients	Serum AST, ALT, and ALP levels↓; MDA levels ↓; TAC and thiols levels↑	Mirzaei et al.[79]
Liver disease	140 mg*3/day	48–50 weeks	78 patients	Legalon was safe at all doses; steatosis and lobular inflammation↓	Navarro et al.[80]
Liver disease	303 mg/day	12 months	116 patients	ELF reduction →; liver stiffness at 6 and 12 months↓	Cossiga et al.[81]
COVID-19	1,050 mg/day	10 days	2 patients	No side effects; patients required minimal oxygen support (2–4 L/min) during the episode	Bosch-Barrera et al.[82,83]
Type 2 diabetes	200 mg*3/day	4 months	51 patients	HbA1c and FBS↓; total cholesterol, triglyceride↓; LDL, SGOT, SGPT↓	Huseini et al.[84]
Type 2 diabetes	140 mg*3/day	45 days	40 patients	Fasting blood sugar, serum insulin, and serum triglyceride↓; triglyceride to high-density lipoprotein cholesterol ratio↓	Ebrahimpour-koujan et al.[85]
Type 2 diabetes	200 mg*3/day	3 months	60 patients	Fasting blood glucose↓; glycosylated hemoglobin↓; triglyceride↓	Khalili et al.[86]
β-thalassemia major	140 mg*3/day	12 weeks	82 patients	CRP and IL-6↓; IL-10↑	Darvishi-Khezri et al.[87]
β-thalassemia major	140 mg*3/day	12 weeks	82 patients	Serum iron and ferritin levels↓; total iron-binding capacity↑	Darvishi-Khezri et al.[88]
β-thalassemia major	420 mg/day	3 months	69 patients	Serum MDA and protein CO↓; serum TAC and plasma GSH↑	Darvishi-Khezri et al.[89]
β-thalassemia intermedia	420 mg/day	6 months	10 patients	Serum ferritin↓	Reisi et al.[90]
Hand-foot syndrome	1% silymarin	9 weeks	40 patients	Median WHO HFS scores↓; the onset and progression of HFS were delayed	Elyasi et al.[91]
Acute lymphoblastic leukemia	420 mg/day	1 week	80 children	Early doxorubicin-induced left; ventricular systolic dysfunction↓	Hagag et al.[92]

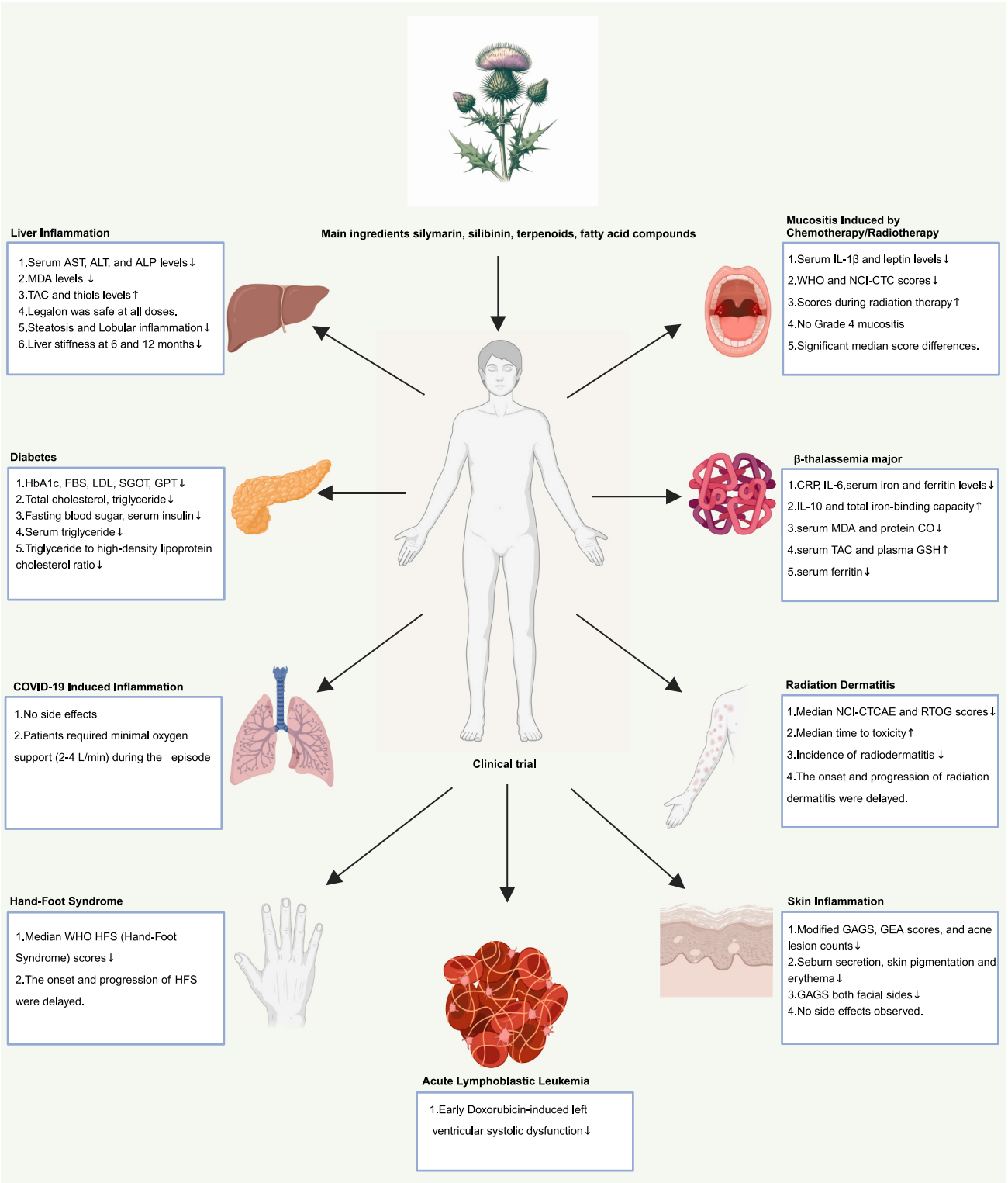

Figure 3. Clinical applications of silymarin as an anti-inflammatory agent

Silymarin can play a role in the clinical treatment of radiotherapy-induced mucositis, radiation dermatitis, skin inflammation, liver inflammation, COVID-19-induced inflammation, diabetes, and β-thalassemia major, among other diseases, through anti-inflammatory mechanisms.

Liver inflammation

Silymarin, recognized for its hepatoprotective properties, has been explored in clinical trials for its efficacy in treating liver inflammation.[95,96] In one study, silymarin administration resulted in a significant reduction in serum malondialdehyde (MDA) levels, indicating lower oxidative stress in the silymarin group compared to controls and highlighting its antioxidant and anti-inflammatory effects.[79] In the context of NASH, silymarin intake ranging from 140 to 700 mg demonstrated safety and tolerability, with an improvement in hepatic steatosis and lobular inflammation observed in some subjects, although these changes did not reach statistical significance in histological improvement.[80] For patients with cirrhosis, a 12-month regimen of Realsil 100D, comprising silymarin, vitamin D, and vitamin E, significantly improved liver stiffness, suggesting an amelioration of liver fibrosis. Additionally, a reduction in platelet-activating factor expression among cirrhotic patients treated with silymarin compared to controls points to its potential to modulate inflammatory pathways and reduce the genotoxic impact of ROS.[81]

COVID-19-induced inflammation

Silibinin, a key component of silymarin, has been identified as a potent inhibitor of signal transducer and activator of transcription 3 (STAT3), a critical regulator of cytokine signaling and immune responses.[97] This inhibition is significant in the context of COVID-19, where IL-6-mediated STAT3 overactivation contributes to the cytokine storm observed in severe cases.[82] Computational studies, including molecular docking and dynamics, have elucidated the interaction between silibinin and STAT3, suggesting a molecular basis for its therapeutic effect. A pilot clinical trial conducted by the Catalan Institute of Oncology evaluated the efficacy of Legalon, a silymarin-based formulation, in patients with COVID-19 with underlying tumors. The administration of 1,050 mg/d of Legalon for ten days was associated with improved clinical outcomes, including reduced oxygen requirements and amelioration of lung lesions, without any reported side effects.[83] These preliminary results underscore the potential of silymarin to modulate inflammatory responses in COVID-19, warranting further large-scale clinical trials to confirm its efficacy.

Diabetes

In two separate studies focusing on type 2 diabetes mellitus (T2DM), silymarin showed considerable benefits. Over four months, one study revealed that silymarin significantly lowered key metabolic markers such as glycated hemoglobin (HbA1c), fasting blood sugar (FBS), total cholesterol, low-density lipoprotein, triglycerides, and liver enzymes, indicating its potential to improve blood sugar and lipid control in patients with T2DM.[84] In another triple-blind trial, silymarin supplementation notably reduced fasting glucose, serum insulin, insulin resistance, and triglyceride levels, further confirming its therapeutic advantages.[85] Moreover, a study on an herbal mix including silymarin, stinging nettle, and frankincense showed that this combination significantly decreased fasting glucose, HbA1c, and triglycerides compared to a placebo, highlighting the efficacy of herbal combinations in enhancing diabetes management.[86]

β-thalassemia major

Patients with severe β-thalassemia major (β-TM) frequently experience inflammation due to iron overload.[98] Studies show that silymarin significantly reduces inflammation markers like C-reactive protein (CRP) and IL-6, while boosting IL-10 levels, suggesting that it could enhance standard iron chelation therapy.[87] Although additional research noted improvements in cardiac and liver functions with silymarin, these were not statistically significant.[88] In a randomized controlled trial, silymarin also reduced oxidative stress and increased antioxidant capacity in patients with β-TM.[89] In those with β-thalassemia intermedia, silymarin effectively lowered ferritin levels after three to six months, highlighting its potential as a natural iron chelator.[90]

Other diseases

Silymarin's therapeutic applications extend beyond liver protection to managing side effects of chemotherapy, such as hand-foot syndrome (HFS), a painful condition affecting patients on capecitabine. A double-blind, placebo-controlled trial demonstrated that topical application of 1% silymarin gel significantly alleviated HFS symptoms, delaying its onset and progression.[91] Furthermore, in a study involving pediatric patients with acute lymphoblastic leukemia, the addition of silymarin to adriamycin therapy mitigated early cardiac dysfunction and reduced troponin levels, indicative of its cardioprotective properties.[92] These outcomes suggest silymarin's potential in enhancing antioxidant defenses and modulating signaling pathways, such as phosphoinositide 3-kinase/protein kinase B (AKT), to exert its protective effects against chemotherapy-induced toxicities.

CONCLUSION

Recently, silymarin exhibits therapeutic potential as a natural anti-inflammatory medicine. The comprehensive understanding of silymarin's anti-inflammatory molecular mechanism and clinical application was included in this review. We focus on the priority that should be given to enhancing silymarin's bioavailability and stability, alongside detailed mechanistic studies, to cement its place in clinical therapeutics for inflammatory diseases. This effort will not only elucidate its role at the molecular level but also provide an experimental basis for silymarin's anti-inflammatory clinical application.

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AUTHOR CONTRIBUTIONS

Y. Zhao: writing – original draft, visualization, formal analysis, investigation, and data curation; Y. Zhou: writing – original draft, visualization, methodology, investigation, funding acquisition, and supervision; T.G.: visualization and data curation; Z.L.: visualization and data curation; W.Y.: data curation; Y.X.: investigation; D.X.: funding acquisition; W.L.: funding acquisition, project administration, and supervision; A.C.: funding acquisition, project administration, and supervision; E.I.: funding acquisition, project administration, and supervision.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Akhtar, M.N., Saeed, R., Saeed, F., Asghar, A., Ghani, S., Ateeq, H., Ahmed, A., Rasheed, A., Afzaal, M., Waheed, M., et al. (2023). Silymarin: a review on paving the way towards promising pharmacological agent. Int. J. Food Prop. *26*, 2256–2272. https://doi.org/10.1080/10942912.2023.2244685.
2. Surai, P.F. (2015). Silymarin as a Natural Antioxidant: An Overview of the Current Evidence and Perspectives. Antioxidants *4*, 204–247. https://doi.org/10.3390/antiox4010204.
3. Ahmed, R.F., Moussa, R.A., Eldemerdash, R.S., Zakaria, M.M., and Abdel-Gaber, S.A. (2019). Ameliorative effects of silymarin on HCl-induced acute lung injury in rats; role of the Nrf-2/HO-1 pathway. Iran J. Basic Med. Sci. *22*, 1483. https://doi.org/10.22038/IJBMS.2019.14069.
4. Jaffar, H.M., Al-Asmari, F., Khan, F.A., Rahim, M.A., and Zongo, E. (2024). Silymarin: Unveiling its pharmacological spectrum and therapeutic potential in liver diseases—A comprehensive narrative review. Food Sci. Nutr. *12*, 3097–3111. https://doi.org/10.1002/fsn3.4010.
5. Kren, V., Marhol, P., Purchartová, K., Gabrielová, E., and Modriansky, M. (2013). Biotransformation of Silybin and its Congeners. Curr. Drug Metab. *14*, 1009–1021. https://doi.org/10.2174/13892002146661311182345O7.
6. Mohammadi, S., Asbaghi, O., Afrisham, R., Farrokhi, V., Jadidi, Y., Mofidi, F., and Ashtary-Larky, D. (2024). Impacts of Supplementation with Silymarin on Cardiovascular Risk Factors: A Systematic Review and Dose–Response Meta-Analysis. Antioxidants *13*, 390. https://doi.org/10.3390/antiox13040390.
7. Palit, P., Mukhopadhyay, A., and Chattopadhyay, D. (2021). Phyto-pharmacological perspective of Silymarin: A potential prophylactic or therapeutic agent for COVID-19, based on its promising immunomodulatory, anti-coagulant and anti-viral property. Phytother Res. *35*, 4246–4257. https://doi.org/10.1002/ptr.7084.
8. Peng, Y., Ao, M., Dong, B., Jiang, Y., Yu, L., Chen, Z., Hu, C., and Xu, R. (2021). Anti-Inflammatory Effects of Curcumin in the Inflammatory Diseases: Status, Limitations and Countermeasures. Drug Des. Dev. Ther. *15*, 4503–4525. https://doi.org/10.2147/dddt.S327378.
9. Wadhwa, K., Pahwa, R., Kumar, M., Kumar, S., Sharma, P.C., Singh, G., Verma, R., Mittal, V., Singh, I., Kaushik, D., and Jeandet, P. (2022). Mechanistic Insights into the Pharmacological Significance of Silymarin. Molecules *27*, 5327. https://doi.org/10.3390/molecules27165327.
10. Girardi, B., Principi, M., Pricci, M., Giorgio, F., Iannone, A., Losurdo, G., Ierardi, E., Di Leo, A., and Barone, M. (2018). Chemoprevention of inflammation-related colorectal cancer by silymarin-acetyl-11-keto-beta-boswellic acid-curcumin- and maltodextrin-enriched dietetic formulation in animal model. Carcinogenesis *39*, 1274–1282. https://doi.org/10.1093/carcin/bgy104.
11. Yardım, A., Kucukler, S., Özdemir, S., Çomaklı, S., Caglayan, C., Kandemir, F.M., and Çelik, H. (2021). Silymarin alleviates docetaxel-induced central and peripheral neurotoxicity by reducing oxidative stress, inflammation and apoptosis in rats. Gene *769*, 145239. https://doi.org/10.1016/j.gene.2020.145239.
12. Singh, G., Mittra, N., and Singh, C. (2023). Tempol and silymarin rescue from zinc-induced degeneration of dopaminergic neurons through modulation of oxidative stress and inflammation. Mol. Cell. Biochem. *478*, 1705–1718. https://doi.org/10.1007/s11010-022-04620-z.
13. Deng, L., He, S., Guo, N., Tian, W., Zhang, W., and Luo, L. (2023). Molecular mechanisms of ferroptosis and relevance to inflammation. Inflamm. Res. *72*, 281–299. https://doi.org/10.1007/s00011-022-01672-1.
14. Karin, M., and Shalapour, S. (2022). Regulation of antitumor immunity by inflammation-induced epigenetic alterations. Cell. Mol. Immunol. *19*, 59–66. https://doi.org/10.1038/s41423-021-00756-y.
15. Kolawole, O.R., and Kashfi, K. (2022). NSAIDs and Cancer Resolution: New Paradigms beyond Cyclooxygenase. Int. J. Mol. Sci. *23*, 1432. https://doi.org/10.3390/ijms23031432.
16. Sokolowska, P., Bleibel, L., Owczarek, J., and Wiktorowska-Owczarek, A. (2024). PPARgamma, NF-kappaB and the UPR pathway as new molecular targets in the anti-inflammatory actions of NSAIDs: Novel applications in cancers and central nervous system diseases? Adv. Clin. Exp. Med. *33*, 1007. https://doi.org/10.17219/acem/174243.
17. Jaber, D., Al Shihab, A., and Tamimi, L.N. (2024). Efficacy and Safety of Pharmacist-Managed NSAIDs Deprescribing: A Jordanian Outpatient Study. J. Clin. Pharm. Ther. *2024*, 5874686. https://doi.org/10.1155/2024/5874686.
18. El-Kot, S.M., Wanas, W., Hafez, A.M., Mahmoud, N.A., Tolba, A.M., Younis, A.H., Sayed, G.E., and Abdelwahab, H.E. (2023). Effect of silymarin on the relative gene expressions of some inflammatory cytokines in the liver of CCl4-intoxicated male rats. Sci. Rep. *13*, 15245. https://doi.org/10.1038/s41598-023-42250-7.
19. Rahimi, D., Sharifi, R., Jaberie, H., and Naghibalhossaini, F. (2024). Antiproliferative and Antitelomerase Effects of Silymarin on Human Colorectal and Hepatocellular Carcinoma Cells. Planta Med. *90*, 298–304. https://doi.org/10.1055/a-2244-8788.
20. Mi, X.-J., Le, H.-M., Lee, S., Park, H.-R., and Kim, Y.-J. (2022). Silymarin-Functionalized Selenium Nanoparticles Prevent LPS-Induced Inflammatory Response in RAW264.7 Cells through Downregulation of the PI3K/Akt/NF-κB Pathway. ACS Omega *7*, 42723–42732. https://doi.org/10.1021/acsomega.2c04140.
21. Tvrdý, V., Pourová, J., Jirkovský, E., Křen, V., Valentová, K., and Mladěnka, P. (2021). Systematic review of pharmacokinetics and potential pharmacokinetic interactions of flavonolignans from silymarin. Med. Res. Rev. *41*, 2195–2246. https://doi.org/10.1002/med.21791.
22. Levien, T.L., and Baker, D.E. (2024). Acetaminophen/Ibuprofen Injection. Hosp. Pharm. *59*, 385–393. https://doi.org/10.1177/00185787241236439.
23. Calatayud, S., and Esplugues, J.V. (2016). Chemistry, Pharmacodynamics, and Pharmacokinetics of NSAIDs. In NSAIDs and Aspirin: Recent Advances and Implications for Clinical Management, A. Lanas, ed. (Springer International Publishing), pp. 3–16. https://doi.org/10.1007/978-3-319-33889-7_1.
24. Macit, M., Duman, G., Cumbul, A., Sumer, E., and Macit, C. (2023). Formulation development of Silybum marianum seed extracts and silymarin nanoparticles, and evaluation of hepatoprotective effect. J. Drug Deliv. Sci. Technol. *83*, 104378. https://doi.org/10.1016/j.jddst.2023.104378.
25. Ahmad, S., Khan, J.A., Kausar, T.N., Mahnashi, M.H., Alasiri, A., Alqahtani, A.A., Alqahtani, T.S., Walbi, I.A., Alshehri, O.M., Elnoubi, O.A., et al. (2023). Preparation, Characterization and Evaluation of Flavonolignan Silymarin Effervescent Floating Matrix Tablets for Enhanced Oral Bioavailability. Molecules *28*, 2606. https://doi.org/10.3390/molecules28062606.

26. Patra, J.K., Das, G., Fraceto, L.F., Campos, E.V.R., Rodriguez-Torres, M.d.P., Acosta-Torres, L.S., Diaz-Torres, L.A., Grillo, R., Swamy, M.K., Sharma, S., et al. (2018). Nano based drug delivery systems: recent developments and future prospects. J. Nanobiotechnol. *16*, 71. https://doi.org/10.1186/s12951-018-0392-8.
27. Li, Z., Jiang, H., Xu, C., and Gu, L. (2015). A review: Using nanoparticles to enhance absorption and bioavailability of phenolic phytochemicals. Food Hydrocolloids *43*, 153–164. https://doi.org/10.1016/j.foodhyd.2014.05.010.
28. Yang, G., Zhao, Y., Zhang, Y., Dang, B., Liu, Y., and Feng, N. (2015). Enhanced oral bioavailability of silymarin using liposomes containing a bile salt: preparation by supercritical fluid technology and evaluation *in vitro* and *in vivo*. Int. J. Nanomed. *10*, 6633–6644. https://doi.org/10.2147/ijn.S92665.
29. Di Costanzo, A., and Angelico, R. (2019). Formulation Strategies for Enhancing the Bioavailability of Silymarin: The State of the Art. Molecules *24*, 2155. https://doi.org/10.3390/molecules24112155.
30. Liu, Z., Sun, M., Wang, Y., Zhang, L., Zhao, H., and Zhao, M. (2018). Silymarin attenuated paraquat-induced cytotoxicity in macrophage by regulating Trx/TXNIP complex, inhibiting NLRP3 inflammasome activation and apoptosis. Toxicol. Vitro *46*, 265–272. https://doi.org/10.1016/j.tiv.2017.10.017.
31. Zhu, Z., and Sun, G. (2018). Silymarin mitigates lung impairments in a rat model of acute respiratory distress syndrome. Inflammopharmacology *26*, 747–754. https://doi.org/10.1007/s10787-017-0407-3.
32. Zhao, X., Wang, H., Yang, Y., Gou, Y., Wang, Z., Yang, D., and Li, C. (2021). Protective Effects of Silymarin Against D-Gal/LPS-Induced Organ Damage and Inflammation in Mice. Drug Des. Dev. Ther. *15*, 1903–1914. https://doi.org/10.2147/dddt.S305033.
33. Matias, M.L., Gomes, V.J., Romao-Veiga, M., Ribeiro, V.R., Nunes, P.R., Romagnoli, G.G., Peracoli, J.C., and Peracoli, M.T.S. (2019). Silibinin Downregulates the NF-κB Pathway and NLRP1/NLRP3 Inflammasomes in Monocytes from Pregnant Women with Preeclampsia. Molecules *24*, 1548. https://doi.org/10.3390/molecules24081548.
34. Tao, Q., and Li, J. (2023). Progress on the research of inflammation and disease. J. Chin. Veter. Med. *42*, 1–16. https://doi.org/10.13823/j.cnki.jtcvm.2023.092.
35. Strowig, T., Henao-Mejia, J., Elinav, E., and Flavell, R. (2012). Inflammasomes in health and disease. Nature *481*, 278–286. https://doi.org/10.1038/nature10759.
36. Lim, J.-O., Shin, N.-R., Seo, Y.-S., Nam, H.-H., Ko, J.-W., Jung, T.-Y., Lee, S.-J., Kim, H.-J., Cho, Y.-K., Kim, J.-C., et al. (2020). Silibinin Attenuates Silica Dioxide Nanoparticles-Induced Inflammation by Suppressing TXNIP/MAPKs/AP-1 Signaling. Cells *9*, 678. https://doi.org/10.3390/cells9030678.
37. Juráňová, J., Aury-Landas, J., Boumediene, K., Baugé, C., Biedermann, D., Ulrichová, J., and Franková, J. (2018). Modulation of Skin Inflammatory Response by Active Components of Silymarin. Molecules *24*, 123. https://doi.org/10.3390/molecules24010123.
38. Zheng, Y., Chen, J., Wu, X., Zhang, X., Hu, C., Kang, Y., Lin, J., Li, J., Huang, Y., Zhang, X., and Li, C. (2022). Enhanced Anti-Inflammatory Effects of Silibinin and Capsaicin Combination in Lipopolysaccharide-Induced RAW264.7 Cells by Inhibiting NF-κB and MAPK Activation. Front. Chem. *10*, 934541. https://doi.org/10.3389/fchem.2022.934541.
39. Sun, S.-C. (2017). The non-canonical NF-κB pathway in immunity and inflammation. Nat. Rev. Immunol. *17*, 545–558. https://doi.org/10.1038/nri.2017.52.
40. Yassin, N.Y.S., AbouZid, S.F., El-Kalaawy, A.M., Ali, T.M., Elesawy, B.H., and Ahmed, O.M. (2021). Tackling of Renal Carcinogenesis in Wistar Rats by Silybum marianum Total Extract, Silymarin, and Silibinin via Modulation of Oxidative Stress, Apoptosis, Nrf2, PPARγ, NF-κB, and PI3K/Akt Signaling Pathways. Oxid. Med. Cell. Longev. *2021*, 7665169. https://doi.org/10.1155/2021/7665169.
41. O'Donnell, A., Pepper, C., Mitchell, S., and Pepper, A. (2023). NF-kB and the CLL microenvironment. Front. Oncol. *13*, 1169397. https://doi.org/10.3389/fonc.2023.1169397.
42. Zinatizadeh, M.R., Schock, B., Chalbatani, G.M., Zarandi, P.K., Jalali, S.A., and Miri, S.R. (2021). The Nuclear Factor Kappa B (NF-kB) signaling in cancer development and immune diseases. Genes Dis. *8*, 287–297. https://doi.org/10.1016/j.gendis.2020.06.005.
43. Bahari, H., Shahraki Jazinaki, M., Rashidmayvan, M., Taheri, S., Amini, M.R., and Malekahmadi, M. (2024). The effects of silymarin consumption on inflammation and oxidative stress in adults: a systematic review and meta-analysis. Inflammopharmacology *32*, 949–963. https://doi.org/10.1007/s10787-023-01423-6.
44. Tian, L., Li, W., and Wang, T. (2017). Therapeutic effects of silibinin on LPS-induced acute lung injury by inhibiting NLRP3 and NF-κB signaling pathways. Microb. Pathog. *108*, 104–108. https://doi.org/10.1016/j.micpath.2017.05.011.
45. Cho, K., Lee, H.G., Piao, J.-Y., Kim, S.-J., Na, H.-K., and Surh, Y.-J. (2021). Protective Effects of Silibinin on Helicobacter pylori-induced Gastritis: NF-κB and STAT3 as Potential Targets. J. Cancer Prev. *26*, 118–127. https://doi.org/10.15430/JCP.2021.26.2.118.
46. Ou, Q., Weng, Y., Wang, S., Zhao, Y., Zhang, F., Zhou, J., and Wu, X. (2018). Silybin Alleviates Hepatic Steatosis and Fibrosis in NASH Mice by Inhibiting Oxidative Stress and Involvement with the Nf-κB Pathway. Dig. Dis. Sci. *63*, 3398–3408. https://doi.org/10.1007/s10620-018-5268-0.
47. Zarpou, S., Mosavi, H., Bagheri, A., Malekzadeh Shafaroudi, M., and Khonakdar-Tarsi, A. (2021). NF-κB and NLRP3 gene expression changes during warm hepatic ischemia-reperfusion in rats with and without silibinin. Gastroenterol. Hepatol. Bed Bench *14*, 267–275.
48. Pisoschi, A.M., Iordache, F., Stanca, L., Cimpeanu, C., Furnaris, F., Geicu, O.I., Bilteanu, L., and Serban, A.I. (2024). Comprehensive and critical view on the anti-inflammatory and immunomodulatory role of natural phenolic antioxidants. Eur. J. Med. Chem. *265*, 116075. https://doi.org/10.1016/j.ejmech.2023.116075.
49. Chakraborty, J., Chakraborty, S., Chakraborty, S., and Narayan, M.N. (2023). Entanglement of MAPK pathways with gene expression and its omnipresence in the etiology for cancer and neurodegenerative disorders. Biochim. Biophys. Acta. Gene Regul. Mech. *1866*, 194988. https://doi.org/10.1016/j.bbagrm.2023.194988.
50. Nadel, G., Maik-Rachline, G., and Seger, R. (2023). JNK Cascade-Induced Apoptosis—A Unique Role in GqPCR Signaling. Int. J. Mol. Sci. *24*, 13527. https://doi.org/10.3390/ijms241713527.
51. Kim, T.-W., Michniewicz, M., Bergmann, D.C., and Wang, Z.-Y. (2012). Brassinosteroid regulates stomatal development by GSK3-mediated inhibition of a MAPK pathway. Nature *482*, 419–422. https://doi.org/10.1038/nature10794.
52. Yue, J., and López, J.M. (2020). Understanding MAPK Signaling Pathways in Apoptosis. Int. J. Mol. Sci. *21*, 2346. https://doi.org/10.3390/ijms21072346.
53. Verma, A., Jakhar, R., Kumar, D., Kumar, V., Dhillon, T., Dangi, M., and Chhillar, A.K. (2023). A computational approach to discover antioxidant and anti-inflammatory attributes of silymarin derived from Silybum marianum by comparison with hydroxytyrosol. J. Biomol. Struct. Dyn. *41*, 11101–11121. https://doi.org/10.1080/07391102.2022.2159879.
54. Huang, G.-J., Deng, J.-S., Chiu, C.-S., Liao, J.-C., Hsieh, W.-T., Sheu, M.-J., and Wu, C.-H. (2012). Hispolon Protects against Acute Liver Damage in the Rat by Inhibiting Lipid Peroxidation, Proinflammatory Cytokine, and Oxidative Stress and Downregulating the Expressions of iNOS, COX-2, and MMP-9. Evid. Base Compl. Alternative Med. *2012*, 480714. https://doi.org/10.1155/2012/480714.
55. Tabaa, M.M.E., Aboalazm, H.M., Shaalan, M., and Khedr, N.F. (2022). Silymarin constrains diacetyl-prompted oxidative stress and neuroinflammation in rats: involvements of Dyn/GDNF and MAPK signaling pathway. Inflammopharmacology *30*, 961–980. https://doi.org/10.1007/s10787-022-00961-9.
56. Yang, F., Jia, M., Deng, C., Xiao, B., Dai, R., and Xiang, Y. (2022). Silibinin ameliorates cisplatin-induced acute kidney injury via activating Nfe2l1-mediated antioxidative response to suppress the ROS/MAPK signaling pathway. J. Mol. Histol. *53*, 729–740. https://doi.org/10.1007/s10735-022-10089-3.
57. Song, J., Pan, W., Sun, Y., Han, J., Shi, W., and Liao, W. (2017). Aspergillus fumigatus-induced early inflammatory response in pulmonary microvascular endothelial cells: Role of p38 MAPK and inhibition by silibinin. Int. Immunopharmacol. *49*, 195–202. https://doi.org/10.1016/j.intimp.2017.05.038.
58. Aghemo, A., Alekseeva, O.P., Angelico, F., Bakulin, I.G., Bakulina, N.V., Bordin, D., Bueverov, A.O., Drapkina, O.M., Gillessen, A., Kagarmanova, E.M., et al. (2022). Role of silymarin as antioxidant in clinical management of chronic liver diseases: a narrative review. Ann. Med. *54*, 1548–1560. https://doi.org/10.1080/07853890.2022.2069854.
59. Surai, P.F. (2023). Chapter 22 - Silymarin as a Vitagene Modulator: Effects on Mitochondria Integrity in Stress Conditions. In Molecular Nutrition and Mitochondria, S.M. Ostojic, ed. (Academic Press), pp. 535–559. https://doi.org/10.1016/B978-0-323-90256-4.00007-2.
60. Rasha Mamdouh, S., and Sara Gamal, T. (2023). Silymarin attenuates escitalopram (cipralex) induced pancreatic injury in adult male albino rats: a biochemical, histological, and immunohistochemical approach. Anat. Cell Biol. *56*, 122–136. https://doi.org/10.5115/acb.22.204.
61. Bijak, M., and Saluk-Bijak, J. (2017). Flavonolignans inhibit the arachidonic acid

pathway in blood platelets. BMC Compl. Alternative Med. *17*, 396. https://doi.org/10.1186/s12906-017-1897-7.
62. Hanna, V.S., and Hafez, E.A.A. (2018). Synopsis of arachidonic acid metabolism: A review. J. Adv. Res. *11*, 23–32. https://doi.org/10.1016/j.jare.2018.03.005.
63. Hung, C.-C., Lee, Y.-H., Kuo, Y.-M., Hsu, P.-C., Tsay, H.-J., Hsu, Y.-T., Lee, C.-C., Liang, J.-J., and Shie, F.-S. (2019). Soluble epoxide hydrolase modulates immune responses in activated astrocytes involving regulation of STAT3 activity. J. Neuroinflammation *16*, 123. https://doi.org/10.1186/s12974-019-1508-2.
64. Saraf, P., Nath Tripathi, P., Kumar Tripathi, M., Tripathi, A., Verma, H., Kumar Waiker, D., Singh, R., and Kumar Shrivastava, S. (2022). Novel 5,6-diphenyl-1,2,4-triazine-3-thiol derivatives as dual COX-2/5-LOX inhibitors devoid of cardiotoxicity. Bioorg. Chem. *129*, 106147. https://doi.org/10.1016/j.bioorg.2022.106147.
65. Anthony, K.P., and Saleh, M.A. (2013). Free Radical Scavenging and Antioxidant Activities of Silymarin Components. Antioxidants *2*, 398–407. https://doi.org/10.3390/antiox2040398.
66. Ni, X., and Wang, H. (2016). Silymarin attenuated hepatic steatosis through regulation of lipid metabolism and oxidative stress in a mouse model of nonalcoholic fatty liver disease (NAFLD). Am. J. Transl. Res. *8*, 1073–1081.
67. Mai, D., Yang, C., Xue, Y., Wang, Y., and Yan, C. (2017). Investigation on silymarin impact on lipopolysaccharide induced inflammation model based on arachidonic acid metabolism pathway. Chin. J. Chromatogr. *35*, 578–586. https://doi.org/10.3724/SP.J.1123.2017.01026.
68. Alsaggar, M., Bdour, S., Ababneh, Q., El-Elimat, T., Qinna, N., and Alzoubi, K.H. (2020). Silibinin attenuates adipose tissue inflammation and reverses obesity and its complications in diet-induced obesity model in mice. BMC Pharmacol. Toxicol. *21*, 8. https://doi.org/10.1186/s40360-020-0385-8.
69. Chen, Y.-H., Lin, H., Wang, Q., Hou, J.-W., Mao, Z.-J., and Li, Y.-G. (2020). Protective role of silibinin against myocardial ischemia/reperfusion injury-induced cardiac dysfunction. Int. J. Biol. Sci. *16*, 1972–1988. https://doi.org/10.7150/ijbs.39259.
70. Shen, H.-H., Alex, R., Bellner, L., Raffaele, M., Licari, M., Vanella, L., Stec, D.E., and Abraham, N.G. (2020). Milk thistle seed cold press oil attenuates markers of the metabolic syndrome in a mouse model of dietary-induced obesity. J. Food Biochem. *44*, e13522. https://doi.org/10.1111/jfbc.13522.
71. Faixová, D., Ratvaj, M., Maruščáková, I.C., Hrčková, G., Karaffová, V., Faixová, Z., and Mudroňová, D. (2023). Silybin Showed Higher Cytotoxic, Antiproliferative, and Anti-Inflammatory Activities in the CaCo Cancer Cell Line while Retaining Viability and Proliferation in Normal Intestinal IPEC-1 Cells. Life *13*, 492. https://doi.org/10.3390/life13020492.
72. Altaei, T.S. (2012). 473P - Treatment of Chemotherapy-Induced Oral Mucositis by Silymarin. Ann. Oncol. *23*, ix163. https://doi.org/10.1016/S0923-7534(20)33033-7.
73. Elyasi, S., Hosseini, S., Niazi Moghadam, M.R., Aledavood, S.A., and Karimi, G. (2016). Effect of Oral Silymarin Administration on Prevention of Radiotherapy Induced Mucositis: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. Phytother Res. *30*, 1879–1885. https://doi.org/10.1002/ptr.5704.
74. Hosseini, S., Rezaei, S., Moghaddam, M.R.N., Elyasi, S., and Karimi, G. (2021). Evaluation of oral nano-silymarin formulation efficacy on prevention of radiotherapy induced mucositis: A randomized, double-blinded, placebo-controlled clinical trial. PharmaNutrition *15*, 100253. https://doi.org/10.1016/j.phanu.2021.100253.
75. Karbasforooshan, H., Hosseini, S., Elyasi, S., Fani Pakdel, A., and Karimi, G. (2019). Topical silymarin administration for prevention of acute radiodermatitis in breast cancer patients: A randomized, double-blind, placebo-controlled clinical trial. Phytother Res. *33*, 379–386. https://doi.org/10.1002/ptr.6231.
76. Becker-Schiebe, M., Mengs, U., Schaefer, M., Bulitta, M., and Hoffmann, W. (2011). Topical Use of a Silymarin-Based Preparation to Prevent Radiodermatitis. Strahlenther. Onkol. *187*, 485–491. https://doi.org/10.1007/s00066-011-2204-z.
77. Atallah, D.A.-A., Badran, A.Y., Makhlouf, A.G., and Mekkawy, M.M. (2024). Topical Silymarin Cream as a Novel Therapy Versus Salicylic Acid Peels in Acne Vulgaris: A Split-Face Clinical Trial. J. Cutan. Med. Surg. *28*, 22–28. https://doi.org/10.1177/12034754231211568.
78. Kim, J., Lee, Y.N., Lee, J., Lee, S.G., Kim, H., Choi, Y.S., Draelos, Z.D., and Kim, J. (2023). Efficacy and safety of silymarin containing antioxidant serum as an adjuvant treatment of mild-to-moderate acne vulgaris: A prospective, open-label pilot study. J. Cosmet. Dermatol. *22*, 561–568. https://doi.org/10.1111/jocd.15439.
79. Mirzaei, E., Sabetian, G., Masjedi, M., Heidari, R., Mirjalili, M., Dehghanian, A., and Vazin, A. (2021). The effect of silymarin on liver enzymes and antioxidant status in trauma patients in the intensive care unit: a randomized double blinded placebo-controlled clinical trial. Clin. Exp. Hepatol. *7*, 149–155. https://doi.org/10.5114/ceh.2021.107067.
80. Navarro, V.J., Belle, S.H., D'Amato, M., Adfhal, N., Brunt, E.M., Fried, M.W., Reddy, K.R., Wahed, A.S., and Harrison, S.; Silymarin in NASH and C Hepatitis SyNCH Study Group (2019). Silymarin in non-cirrhotics with non-alcoholic steatohepatitis: A randomized, double-blind, placebo controlled trial. PLoS One *14*, e0221683. https://doi.org/10.1371/journal.pone.0221683.
81. Cossiga, V., Sanduzzi-Zamparelli, M., Sapena, V., Guarino, M., Dallio, M., Torrisi, E., Pignata, L., Federico, A., Salomone, F., and Morisco, F. (2022). Beneficial Effects of Silybin Treatment After Viral Eradication in Patients With HCV-Related Advanced Chronic Liver Disease: A Pilot Study. Front. Pharmacol. *13*, 824879. https://doi.org/10.3389/fphar.2022.824879.
82. Bosch-Barrera, J., Martin-Castillo, B., Buxó, M., Brunet, J., Encinar, J.A., and Menendez, J.A. (2020). Silibinin and SARS-CoV-2: Dual Targeting of Host Cytokine Storm and Virus Replication Machinery for Clinical Management of COVID-19 Patients. J. Clin. Med. *9*, 1770. https://doi.org/10.3390/jcm9061770.
83. Bosch-Barrera, J., Roqué, A., Teixidor, E., Carmona-Garcia, M.C., Arbusà, A., Brunet, J., Martin-Castillo, B., Cuyàs, E., Verdura, S., and Menendez, J.A. (2021). Clinical Management of COVID-19 in Cancer Patients with the STAT3 Inhibitor Silibinin. Pharmaceuticals *15*, 19. https://doi.org/10.3390/ph15010019.
84. Huseini, H.F., Larijani, B., Heshmat, R., Fakhrzadeh, H., Radjabipour, B., Toliat, T., and Raza, M. (2006). The efficacy of Silybum marianum (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled, clinical trial. Phytother Res. *20*, 1036–1039. https://doi.org/10.1002/ptr.1988.
85. Ebrahimpour-koujan, S., Gargari, B.P., Mobasseri, M., Valizadeh, H., and Asghari-Jafarabadi, M. (2018). Lower glycemic indices and lipid profile among type 2 diabetes mellitus patients who received novel dose of Silybum marianum (L.) Gaertn. (silymarin) extract supplement: A Triple-blinded randomized controlled clinical trial. Phytomedicine *44*, 39–44. https://doi.org/10.1016/j.phymed.2018.03.050.
86. Khalili, N., Fereydoonzadeh, R., Mohtashami, R., Mehrzadi, S., Heydari, M., and Huseini, H.F. (2017). Silymarin, Olibanum, and Nettle, A Mixed Herbal Formulation in the Treatment of Type II Diabetes: A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial. J. Evid. Based. Compl. Alternative Med. *22*, 603–608. https://doi.org/10.1177/2156587217696929.
87. Darvishi-Khezri, H., Kosaryan, M., Karami, H., Salehifar, E., Mahdavi, M., Alipour, A., and Aliasgharian, A. (2021). Can Use of Silymarin Improve Inflammatory Status in Patients with β-Thalassemia Major? A Crossover, Randomized Controlled Trial. Complement. Med. Res. *28*, 123–130. https://doi.org/10.1159/000509829.
88. Darvishi-Khezri, H., Salehifar, E., Kosaryan, M., Karami, H., Mahdavi, M., Alipour, A., and Aliasgharian, A. (2018). Iron-chelating effect of silymarin in patients with β-thalassemia major: A crossover randomised control trial. Phytother Res. *32*, 496–503. https://doi.org/10.1002/ptr.5995.
89. Darvishi-Khezri, H., Salehifar, E., Kosaryan, M., Karami, H., Alipour, A., Shaki, F., and Aliasgharian, A. (2017). The impact of silymarin on antioxidant and oxidative status in patients with β-thalassemia major: A crossover, randomized controlled trial. Complement. Ther. Med. *35*, 25–32. https://doi.org/10.1016/j.ctim.2017.08.007.
90. Reisi, N., Esmaeil, N., Gharagozloo, M., and Moayedi, B. (2022). Therapeutic potential of silymarin as a natural iron-chelating agent in β-thalassemia intermedia. Clin. Case Rep. *10*, e05293. https://doi.org/10.1002/ccr3.5293.
91. Elyasi, S., Shojaee, F.S.R., Allahyari, A., and Karimi, G. (2017). Topical Silymarin Administration for Prevention of Capecitabine-Induced Hand–Foot Syndrome: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. Phytother Res. *31*, 1323–1329. https://doi.org/10.1002/ptr.5857.
92. Hagag, A.A., El Shehaby, W.A., El-Abasy, A.I., and Mabrouk, M.M. (2018). Protective Role of Silymarin in Early Doxorubicin-induced Cardiac Dysfunction in Children with Acute Lymphoblastic Leukemia. Infect. Disord. Drug Targets *18*, 133–140. https://doi.org/10.2174/1871526518666180803141827.
93. Liu, X., Zhang, W., Chen, Y., Rastogi, S., and Choudhury, R. (2023). Effectiveness of zinc supplementation on the incidence of oral mucositis during chemotherapy and radiation: A meta-analysis. Exp. Ther. Med. *26*, 347. https://doi.org/10.3892/etm.2023.12046.

94. Manfredini, M., Sticchi, A., Lippolis, N., Pedroni, G., Giovani, M., Ciardo, S., Chello, C., Guida, S., Farnetani, F., and Pellacani, G. (2023). Characterization of Acne-Prone Skin with Reflectance Confocal Microscopy and Optical Coherence Tomography and Modifications Induced by Topical Treatment and Probiotic Supplementation. J. Clin. Med. *12*, 4787. https://doi.org/10.3390/jcm12144787.

95. de Avelar, C.R., Nunes, B.V.C., da Silva Sassaki, B., dos Santos Vasconcelos, M., de Oliveira, L.P.M., Lyra, A.C., Bueno, A.A., and de Jesus, R.P. (2023). Efficacy of silymarin in patients with non-alcoholic fatty liver disease — the Siliver trial: a study protocol for a randomized controlled clinical trial. Trials *24*, 177. https://doi.org/10.1186/s13063-023-07210-6.

96. Maryam, T., Rana, N.F., Alshahrani, S.M., Batool, F., Fatima, M., Tanweer, T., Alrdahe, S.S., Alanazi, Y.F., Alsharif, I., Alaryani, F.S., et al. (2023). Silymarin Encapsulated Liposomal Formulation: An Effective Treatment Modality against Copper Toxicity Associated Liver Dysfunction and Neurobehavioral Abnormalities in Wistar Rats. Molecules *28*, 1514. https://doi.org/10.3390/molecules28031514.

97. Verdura, S., Cuyàs, E., Llorach-Parés, L., Pérez-Sánchez, A., Micol, V., Nonell-Canals, A., Joven, J., Valiente, M., Sánchez-Martínez, M., Bosch-Barrera, J., and Menendez, J.A. (2018). Silibinin is a direct inhibitor of STAT3. Food Chem. Toxicol. *116*, 161–172. https://doi.org/10.1016/j.fct.2018.04.028.

98. Rund, D., and Rachmilewitz, E. (2005). β-Thalassemia. N. Engl. J. Med. *353*, 1135–1146. https://doi.org/10.1056/NEJMra050436.